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Pancreatitis

HENRY D. JANOWITZ
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MONTHLY CLINICAL MONOGRAPHS ON CURRENT MEDICAL PROBLEMS

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Pancreatitis

HENRY D. JANOWITZ
DAVID A. DREILING

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IT IS CONVENIENT to consider pancreatitis as the sum of the inflammatory changes occurring within the pancreas: a spectrum which includes the dramatic eruption of acute hemorrhagic necrosis of acute pancreatitis at one end and the protracted debilitating metabolic consequences of chronic pancreatitis at the other end. The convenience of this assumption that the chronic form of this disorder is but the sum of the acute episodes is probably a misleading oversimplification of the fact that what we call "pancreatitis" is the manifestation of a wide variety of disorders.

This article is concerned primarily with the clinical recognition and therapeutic management of inflammatory disorders of the pancreas. It assumes that a rational approach to this group of still-puzzling problems depends on an attempt to sort out the various kinds of pancreatitis.

As a digestive gland the pancreas is concerned with the digestion of the 3 major classes of foodstuffs. This it does by secreting an alkaline fluid composed primarily of bicarbonate, which may reach a concentration up to 150 mEq./L., containing the pancreatic enzymes. The main function of this juice is apparently to adjust the pH of the duodenal contents to that required for the action of the digestive ferments.

For fat digestion, pancreatic lipase in the presence of the emulsifying bile salts of the liver acts on neutral triglyceride fat, liberating varying amounts of mono- and diglycerides, as well as fatty acids and glycerol. Pancreatic amylase splits the complex carbohydrates into simpler sugars. The proteolytic ferments trypsin, chymotrypsin and carboxypeptidase reduce proteins by stages to polypeptides and ultimately to amino acids after they are activated.

The control of pancreatic secretion is complex and still only incompletely understood. Numerous factors (vagal excitatory, sympathetic inhibitory and vasomotor stimuli), and at least two separate humoral factors (secretin stimulating a fluid rich in bicarbonate, and pancreozymin stimulating enzyme secretion), are involved. Secretin is released primarily by acid in the duodenum, and pancreozymin by foodstuffs in the upper gut, but local reflexes are probably also important.

In the past, much emphasis has been placed on the anatomic configuration of the terminations of the common bile duct and the main pancreatic ducts, since a "common channel" has been considered important in the pathogenesis of acute pancreatitis. Anatomic and functional studies indicate that between one third and two thirds of normal subjects have a common channel; however, direct studies of pressure relationships (in animals at least) indicate that the secretory pressures in the pancreatic duct are consistently higher than those found in the biliary tree in the resting state, following meals and after stimulation of bile and pancreatic flow.

Trypsinogen, the main proteolytic enzyme of the pancreas, requires activation by intestinal enterokinase or trypsin itself. Trypsinogen is secreted in the presence of a specific inhibitor, but there is experimental and clinical evidence that some activated trypsin is secreted in inflammatory diseases of the pancreas.

ACUTE PANCREATITIS

Definition

Acute pancreatitis is a chemical autolytic disease process with the escape of activated proteolytic and lipolytic enzymes into the glandular interstitial tissue. The process is one of localized autodigestion and tissue disruption.

The Clinical Picture

Acute pancreatitis varies greatly in the intensity of clinical manifestations. It occurs in almost all age groups, although predominantly in middle life, and almost equally in both sexes. In most instances, the onset is acute, with severe abdominal pain—often following a large meal or some indiscretion in alcoholic intake. The pain extends across the epigastrium from right to left, in keeping with the location of the gland, and transmission to the back is frequent. Marked nausea and vomiting often occur, with subsequent cessation of intestinal activity. True rigor is rare, but fever is present in all patients, often reaching quite high levels. The clinical evidences of shock are readily apparent: hypotension, tachycardia and cyanosis of the nail beds and lips.

The abdomen is tender over the pancreas, with distention. Only rarely can a mass be felt in the pancreas itself. The lungs may reveal basal rales, limitation of diaphragmatic movement and later occasionally a left pleural effusion. In a few instances, there is fullness in the left flank, with costovertebral angle tenderness simulating a perinephric abscess.

The cutaneous manifestations are interesting and of varied significance. About one quarter of the patients have transient jaundice during the course of an acute episode of pancreatitis. Livedo reticularis has been seen on the abdomen and lower extremities. Bluish discoloration of the flanks and of the umbilicus are well known, but may not be noted.

Pathogenesis of the Disease Process

The underlying mechanism in the production of pancreatic inflammation is the escape of activated enzymes into the inter-

stitial tissues. The earliest response is edema, distention of the lymphatics and vascular engorgement of the pancreas. Apparently the interstitial fluid within the pancreas contains potent enzyme inhibitors, because many cases of pancreatic edema are seen surgically without evidence of necrosis. Furthermore, the protease inhibitors appear to be more effective than the antilipases; witness the frequent discovery of fat necrosis in and around the pancreas in the absence of hemorrhage or tissue digestion.

Edema is likely to be more severe in the head of the pancreas, although it may occur anywhere in the gland. The region affected becomes pale, indurated and its blood vessels progressively more congested. The edematous fluid exudes into the interlobular connective tissue and into the acini. It is an inflammatory exudate containing polymorphonuclear leukocytes and round cells. In most instances, this inflammatory exudate subsides spontaneously, but in a small percentage of cases the inflammatory process proceeds to hemorrhage, necrosis and suppuration, or regresses to chronicity. Progression of pancreatic edema to hemorrhagic necrosis is in part the result of swelling of the pancreas within its capsule, a process which further increases or initiates pancreatic duct obstruction, if this is not already present, and which may enhance lymphatic congestion and vascular engorgement until vascular ischemia supervenes. Ischemia may also be the result of reflex vasospasm through the celiac plexus. As elsewhere, ischemia superimposed on an inflammatory process results in infarction; i.e., pancreatic hemorrhage and necrosis. Arterial or venous thrombosis and erosion of major blood vessels by activated pancreatic ferments may result in hemorrhage into the pancreas, the retroperitoneal tissue and even into the bowel, whereinto bleeding has also been noted to arise from: (1) submucosal varices, (2) duodenitis and gastritis, (3) acute peptic ulceration and (4) esophageal varices. The most severe hemorrhage, pancreatic apoplexy, converts the gland into a boggy hematoma. Collections of blood may burrow beneath the capsule of the gland, along the tissue planes into the gastrohepatic ligament and retroperitoneally into the lesser sac and flank. In this manner, necrosis and hemorrhage may extend into the left subphrenic space, along the aorta into the pelvis and to the renal capsule. Further dissection along these planes leads to visible hemorrhagic areas in the costo-

vertebral angle, *Turner's sign* and, within the umbilical region, *Cullen's sign.*

In pancreatic necrosis, the pancreas presents numerous yellow, gray or black and red areas, according to the extent and severity of the processes of pancreatic necrosis, infarction and hemorrhage which occur concomitantly, but in different degrees in different zones. Microscopically, varying stages of cell disintegration can be seen. The cells are pale and their nuclei stain poorly. In the most extensively damaged regions, all structure is lost. Surrounding the areas of necrosis and demarcating them from normal tissues is a zone of debris and a layer of inflammatory cells. Liquefaction of the dead tissue, hemorrhagic collections and retention of blocked pancreatic secretion give rise to cystic structures within the zones of demarcation. The formation of cysts lined with inflammatory cells is a curious feature of the pathology of acute pancreatitis. These cysts may coalesce to form larger sacs displacing the stomach, duodenum or color. They are termed pseudocysts to differentiate them from true pancreatic cysts, which are formed within the pancreatic duct system and are lined with epithelial cells.

Collections of blood, digested tissues and pancreatic secretions accumulate in the peritoneal cavity as the classic ascitic exudate of acute pancreatitis, described as "beef broth." The peritoneal effusion and peritoneal irritation during the early stages of acute pancreatitis are most marked in the lesser sac and at the base of the transverse mesocolon. This localized peritonitis often results in a segmental paralytic ileus of the first jejunal loop which has been described as the "sentinel loop" in acute pancreatitis or even in a functional obstruction of the midtransverse colon, giving rise to the "colon-cutoff" sign. Pleural effusions in the left chest are the reaction to inflammations under the left diaphragmatic leaf.

The local pathology of pancreatitis, thus, at the inception is the result of edema, hemorrhage and the onslaught of the biochemical agents—the pancreatic ferments. As the disease progresses without resolution, infection (especially by the intestinal bacteria, the colon-aerogenes group) produces suppuration and results in pancreatic abscesses, as well as purulent collections in the various abdominal fossae such as the lesser sac, the cul-de-sac and the left subphrenic space. The diffuse peritonitis, previously chemical in

nature, now becomes infectious and results in the formation of adhesions over the gallbladder, the liver, the stomach and the colon. Typically, the foramen of Winslow is obliterated.

Resolution may occur with fibrosis and calcification. The edema and other inflammatory changes subside during the first week of illness. Areas of necrosis are autolyzed and replaced by fibrous tissues. Cellular proliferations attempt to restore normal glandular architecture. As in the liver, the ductular proliferation and reduplication overshadows the acinar restoration, so that the pathology of repair in pancreatic inflammation is dominated by this ductular reduplication and there results a relative increase in the ductular-acinar mass ratio. Occasionally, with obstruction of a duct by fibrosis or by the deposition of a calcium stone within its lumen, a retention cyst may form. By the end of the second week, there may be such extensive anatomic histologic repair that the pancreas appears grossly normal. On the other hand, in the more severe forms of acute pancreatic inflammation, resolution is delayed and residual fibrosis and acinar disruption persist.

"Etiologies" of Pancreatitis

Since the classic papers of Archibald and of Rich and Duff, the etiology of pancreatic inflammatory disease has been the subject of a number of excellent reviews. Whereas the earlier reports deal for the most part with the merits and inconsistencies of the common channel theory, later communications present a broader view of multiple etiologies in the pathogenesis of pancreatitis. Indeed, Sterling enumerated 66 possible etiologic factors. This change in concept has resulted from a better understanding of the physiologic mechanisms in pathogenesis and reflects an attempt to co-ordinate and simplify the multiple factors apparently operative in the diverse clinical forms of pancreatitis. Although there might be some objection to comparing etiologic mechanisms in such divergent clinical syndromes as acute hemorrhagic pancreatitis with the chronic inflammatory fibrosis as seen in nutritional and metabolic disorders, there is experimental, pathologic and clinical evidence that chronic pancreatitis may represent the summation of pathologic residue of repeated attacks of acute pancreatic inflammation, either of clinical or subclinical severity.

In the accompanying table, an attempt has been made to classify the etiologic factors recognized in the pathogenesis of pancreatic

ETIOLOGIC FACTORS IN PANCREATITIS AND THE CORRESPONDING CLINICAL AND EXPERIMENTAL VARIETIES*

ETIOLOGIC FACTOR	CLINICAL VARIETY	EXPERIMENTAL VARIETY
Infectious	Mumps	Coxsackie virus
	? Cholecystic disease	
Mechanical	Acute hemorrhagic, edematous & necrotic pancreatitis	Ductal ligation; secretory stimulation
Common channel Obstruction-hypersecretion	Chronic pancreatitis	Ductal injection
	Cholecystic disease	
	Choledocholithiasis	
	? Alcoholism	
	Hydatid, Clonorchis and Ascaris infestation	
Metabolic-nutritional	Essential hyperlipemia	Ethionine
	Hemachromatosis, siderosis	
	Kwashiorkor and protein deficiencies	Protein-deficient feeding
	Alcoholism, cirrhosis,	
	Sprue, ulcerative colitis, diffuse jejunoileitis	
	Hyperparathyroidism	
	? Pregnancy	
Vascular	Diabetic ketosis	Vascular insufficiency
	Terminal pancreatitis (arteriosclerosis, coronary)	
	Periarteritis, lupus	
Toxic	Methyl alcohol poisoning	Zinc poisoning
		Alloxan
		Cobaltous chloride poisoning
Allergic	Periarteritis nodosa	Arthus and Schwartzman phenomena
Traumatic	External trauma	Incisional
	Operative trauma	Ductal transection
Unclassified	Pregnancy	
	Hodgkin's disease	
	Electric shock	

*Adapted from Dreiling, D. A., and Janowitz, H. D.: A review of modern concepts of pancreatic disease, New York J. Med. 56:2992, 1956.

inflammation and to correlate these with the clinical or experimental varieties of pancreatitis in which each factor is operative.

Infectious factors.—No single infectious agent has ever been isolated from all cases of acute pancreatitis, nor has the transplantation of serum, nasal secretion or duodenal juice from patients with pancreatitis to healthy persons resulted in pancreatitis. Nevertheless, blood-borne infection as an etiology of pancreatitis has been proved experimentally by transmission with Coxsackie virus in animals, and clinically by its presence in typhoid fever, scarlet fever, mumps, streptococcal food poisoning, ileitis ulcerative colitis, dysentery and Candida albicans infections.

Although direct drainage of infection from the lymphatics of a diseased gallbladder has been discarded as a pathway, the common association of chronic gallbladder disease and, what is more salient, the beneficial effect which eradication of biliary tract disease has on co-existing pancreatitis argues strongly for an infectious origin of some pancreatic inflammation. The incidence of biliary tract disease has been reported as high as 70% and about 50% of the patients have biliary tract stones. Cholelithiasis, indeed, is 6 times more prevalent in patients with pancreatitis than in unselected autopsy material.

The manner in which biliary tract disease predisposes to or incites pancreatitis has been the subject of much debate. The proponents of the common channel theory have argued that infection is spread to the pancreas via the bile, so that biliary reflux is the responsible agent. Others have suggested that chronic biliary tract disease affects the pancreas by reflexly inducing pancreatic duct and sphincteric spasm. Some light is shed on the problem by the results of experimental studies which show:

1. That while the injection of bacterial suspension into the pancreatic duct will cause pancreatitis, the injection of sterile solutions will have the same effect.

2. That while the mere presence of bacteria in the pancreatic duct does not always result in pancreatitis, it occasionally does, and, moreover, when combined with other factors which initiate pancreatitis, always markedly increases the severity of pathology.

Thus, while infection as a primary factor is probably of minimal importance in the etiology of pancreatitis, its secondary role may be of considerable consequence in contributing to the clinical

severity of the pancreatitis. This concept has been stressed recently by Persky as a conclusion drawn from the beneficial effects antibiotics were noted to have on the course of clinical and experimental pancreatitis, and by Thal *et al.*, who showed that microorganisms and their toxins produce small vessel thrombotic occlusions in the pancreas and thus add a vascular effect which may convert interstitial inflammation to pancreatic necrosis.

Mechanical factors.—The importance of a mechanical factor in the pathogenesis of pancreatitis has been widely accepted. It was first stressed by Opie, who propounded his "common channel" theory of pancreatitis from the observation of acute pancreatitis in a patient in whom a small calculus had become impacted in the papilla of Vater. Opie postulated, and the subsequent adherents of his thesis supported the concept, that in such anatomic situations it was the retrograde passage or reflux of bile into the pancreatic duct which initiated the pathologic process either through the introduction of infection or by chemical activation of the pancreatic ferments. However, the significance of the "bile factor" in pancreatitis has been challenged from the very beginning because of observations which showed that:

1. Whereas clinically and pathologically pancreatic juice can be demonstrated in the cholecystal and choledochal bile, pathologic and clinical evidence of the presence of bile in the pancreatic duct system of patients with pancreatitis is lacking.
2. The secretory pressure relationships in the biliary and pancreatic tracts argue against the probability of biliary reflux.
3. The experimental diversion in dogs and goats of the entire biliary flow through an unobstructed pancreatic duct system fails to produce pancreatitis.
4. Pancreatitis may occur in patients in whom the common duct and pancreatic duct enter the duodenum separately, so the biliary reflux is not possible.

On the other hand, the "bile factor" cannot be completely discarded. Thal has demonstrated that the presence of bile in the pancreatic ducts and interstitial tissues may initiate pancreatitis through a vascular effect, viz., by inducing vascular stasis by capillary wall injury and arteriolar spasm. Others have reported that during obstruction to pancreatic flow there is an alteration in the pancreatic resistance to activated bile; i.e., bile

admixed with pancreatic juice. The so-called necrotizing toxicity of admixtures of bile and pancreatic juice must be questioned in light of the findings that no injuries to the gallbladder and common ducts followed the anastomosis of the pancreatic duct to the gallbladder in dogs. Finally, significantly in favor of the "bile factor" is the beneficial influence on the symptoms in chronic pancreatitis which Bowers has noted in patients in whom bile is completely diverted from the sphincteric area by a choledochojejunostomy.

The anatomic evidence cited in favor of the common channel theory has been the high incidence of this configuration in autopsy material, and the repeated visualization of the pancreatic ducts in patients with pancreatitis by cholangiography performed through the common duct or through a T tube. Yet it is difficult to explain the results of Mallet-Guy and Guira, who in a series of 2,200 operative cholangiographies demonstrated reflux in 18% of the patients without pancreatitis, whereas among 400 patients with pancreatitis, a common channel was observed in only 12%. Ivy and Gibbs' analytic summary of the literature revealed that the anatomic common channel probably existed in about 70% of the population, and that biliary reflux was possible in about half of these. The more recent studies of Kleitsch, taking into consideration the important relations of the accessory pancreatic duct, have confirmed this estimate, as have our biliary flow data. Ivy and Gibbs reported that the pancreatic ducts were visualized with operative and postoperative cholangiography in about 35% of the patients; yet, it is a curious fact that despite an extensive literature dealing with the visualization of the intact human biliary tract by intravenous cholangiography, there are no reports of pancreatic duct delineation. The strongest anatomic evidence in favor of the common channel theory is present in the clinical experience of Doubilet, who was able to prove the existence of a common channel from the cholangiograms, operative observations and the demonstration of pancreatic reflux into the common duct in 316 of 319 patients with pancreatitis. In this connection, although analysis of the biliary flow indicated a functional common channel in 67.2% of 482 patients without pancreatitis, among 197 patients with pancreatitis, we concluded that a functional common channel was indicated by the biliary flow in

91.9%. This prevalence of common channels in patients with pancreatitis, when contrasted with the much lower estimated incidence in unselected series, requires elucidation by the critics of this etiologic hypothesis.

Because choledocholithiasis could account for only about 5% of the cases of acute pancreatitis, the common channel theory was modified by Archibald, who showed that spasm of the sphincter of Oddi could also produce the anatomic configuration. Since this observation, the sphincteric mechanism has assumed increasing importance in the pathogenesis, and the various factors which influence its tonicity have been implicated in the production of pancreatitis, viz.:

1. Edema due to duodenal inflammation.
2. Chronic inflammatory stenosis, Odditis and hypertrophy.
3. Psychic stimuli.
4. Reflex stimulation from lesions in the biliary tract.
5. Duodenal hyperacidity.
6. Narcotics such as morphine and various parasympathomimetic agents.

A second modification of the common channel theory was made by Rich and Duff, whose studies, like those of Mann and Giordano, demonstrated that it was not bile, per se, which initiated experimental pancreatitis, but rather the pressures under which bile or other substances were injected into the pancreatic duct. When these pressures were great enough, over 500 mm. H_2O, the pancreatic ducts were ruptured and pancreatitis ensued. Rich and Duff stressed that the effective pathogenetic factor in patients with anatomic common channels who develop pancreatitis was the pancreatic duct obstruction rather than the biliary regurgitation. They reported pancreatic duct narrowing due to metaplasia of the ductal epithelium in 13 of 24 patients with acute pancreatitis and in 18.6% of 150 consecutive autopsies. The concept of ductal metaplasia has not gained wide acceptance because of the frequency with which it has been observed in normal postmortem glands and because of its rarity in patients dying of acute pancreatitis. On the other hand, the concept of pancreatic duct obstruction as the mechanical etiology of pancreatitis has been generally acknowledged.

The importance of pancreatic duct obstruction in the genesis

of pancreatitis is illustrated by experimental procedures in which, following ligation of the ducts of Santorini and Wirsung, a stimulus to pancreatic secretion is given. Popper and Necheles produced pancreatitis by feeding or administering secretin; Lium and Maddock used Mecholyl® as the stimulus. With rising intraductal pressures due to secretion against obstruction, there occurs a rupture of the pancreatic duct radicals and an escape of enzymes into the tissues and into the blood stream. Pancreatic duct obstruction, per se, is insufficient to produce pancreatitis. Ligation of the ducts merely leads to pancreatic fibrosis and atrophy. However, when either active secretion or interference of blood flow are added to ductal obstruction, acute pancreatitis regularly follows. The ultimate effect of pancreatic duct obstruction is the development of abnormally high pancreatic duct pressures. The high pressures are the basic means of producing pancreatic duct rupture and are illustrated by the pancreatitis seen after cholangiography.

The clinical evidence in favor of pancreatic duct obstruction as an etiology in pancreatitis arises from:

1. The demonstration of pancreatic duct dilation and obstruction due to calculi and fibrosis in postmortem cases of pancreatitis.

2. The occurrence of chronic inflammatory fibrosis in parasitic infestations, such as Ascaris, Clonorchis and Echinococcus disease, in which the pancreatic ducts are blocked by parasites.

3. The beneficial effect of surgical procedures which relieve this obstruction on the course of clinical and experimental pancreatitis.

Chronic cystic fibrosis of the pancreas is a congenital disorder in which obstruction of the duct system is of etiologic significance. This obstruction is due both to developmental anomaly and to the inspissation of a viscid pancreatic secretion. It has been suggested that fibrocystic disease is due to a complete lack of secretin in the duodenal mucosa. However, subsequent study of postmortem material has failed to corroborate this contention.

Another clinical variety of pancreatitis in which ductal obstruction appears to be an etiologic factor is the pancreatitis associated with alcoholism. This relationship has been stressed since Friedreich's description of the "drunkard's pancreas" in 1878. Much

has been written concerning the high incidence of acute alcoholism in acute pancreatitis and of chronic alcoholism in chronic pancreatitis, the latter ranging from 25 to 75% in reported series. Others have commented on the startling frequency with which acute alcoholism preceded or appeared to precipitate attacks of acute pancreatitis. That mild attacks of pancreatic edema and even subclinical episodes of pancreatitis occur in acute alcoholism is suggested by reports of frequent blood amylase elevations in alcoholics with alcoholic gastritis and delirium tremens. The cumulative effect of such episodes is the chronic pancreatic fibrosis of the chronic alcoholic.

The mechanism whereby alcoholism incites pancreatitis has been much debated. Egdahl suggested that gastroduodenitis might be responsible for the pancreatitis. Probstein believes that alcohol is toxic to the pancreas and that alcoholic pancreatitis is a distinct clinical entity differing in etiology from the nonalcoholic. While methanol can be shown to produce toxic lesions in the pancreas, there is no experimental evidence to show that ethanol is capable of so doing. The following possibilities have been advanced:

1. That alcohol in the blood might stimulate or damage the pancreas directly.
2. That duodenal inflammation might obstruct or infect the pancreatic ducts.
3. That persistent vomiting might cause regurgitation of duodenal contents into the pancreatic ducts or might cause rupture of the pancreatic ductules directly.
4. That alcohol may cause vascular congestion and capillary hemorrhage in the pancreas.

Gizelt has shown that orally ingested alcohol stimulates pancreatic secretion. He believed this action to be the summation of direct stimulation of the gland by the absorbed drug, of direct stimulation of secretin in the duodenum and of an indirect stimulation of secretin secondary to alcohol-induced acid production in the stomach. However, one of us (D.A.D.) demonstrated that intravenous ethyl alcohol in man neither stimulated the pancreatic flow nor had a deleterious effect on patients with or without pancreatitis. Brooks and Thomas confirmed experimentally the inability of alcohol to stimulate pancreatic flow directly,

denied that it stimulated the formation of secretin in the duodenum and attributed its entire pancreatic secretagogue action to its acid-forming properties. The local effect of alcohol in the duodenum and of the alcohol-induced gastric acidity appears to be duodenitis, edema of the papilla and intense spasm of the sphincter of Oddi, actions which synergistically produce an obstruction to pancreatic flow.

An attempt to correlate these physiologic effects of alcohol has led to the hypothesis that following a large alcoholic intake the pancreas would be stimulated via the acid-secretin mechanism to secrete a large volume of juice into a duct obstructed by alcohol-induced papillary edema and sphincter spasm. This mechanical sequence of events is similar to that postulated for the clinical pancreatitis observed to follow gluttony and to the experimental type of pancreatitis produced by Popper and Lium by stimulation of the pancreas after pancreatic duct ligation. Cogent as the mechanical hypothesis may appear, the fact that the severe dietary deficiencies which are associated with chronic alcoholism may contribute significantly to the chronic pancreatic inflammatory changes found in these people must not be overlooked.

Metabolic and nutritional factors.—There is abundant evidence that metabolic and nutritional factors are of etiologic significance in the pathogenesis of pancreatitis. Clinically, pancreatitis has been described in such metabolic disorders as hemochromatosis, generalized siderosis as seen in sicklemia or in Cooley's anemia and essential hyperlipemia. The pancreatic inflammatory changes in hemochromatosis and generalized siderosis are due to the irritating effect of organic iron deposited in the interstitial and glandular tissue of the pancreas. In about half the cases of hemochromatosis impaired external secretion may be demonstrated.

The relationship of abnormal fat metabolism to pancreatitis is more obscure. To be sure, transient hyperlipemia is observed in acute pancreatitis, and hyperlipemia, fatty infiltration of the liver and depletion of the fat reservoirs have been reported in chronic external pancreatic deficiencies and in chronic pancreatitis. These phenomena have been ascribed to "lipocaic" deficiencies and to hyperlipasemia. In Klatskin's cases, however, the hyperlipemia clearly preceded the pancreatitis and did not result from it. It has been suggested that plugging of the pancreatic

arterioles by fat emboli is responsible for the pancreatitis.

Experimentally, the interference with protein metabolism by ethionine induces a metabolic pancreatitis. This should be considered metabolic rather than toxic inasmuch as its pathogenesis may be prevented by the simultaneous or prior administration of methionine.

The nutritional etiology of pancreatitis appears to implicate protein deficiency as the inciting factor. Clinically, pancreatic fibrosis has been seen in the protein deficiency states of kwashiorkor, ulcerative colitis, diffuse jejunoileitis, sprue, cirrhosis and other malnutrition syndromes. Fibrosis and cystic changes in the pancreas have been produced experimentally in animals fed a high-fat, low-protein diet. Finally, a nutritional factor has been considered to contribute to the pancreatitis of alcoholism, and may play a role in the pancreatitis which has been noted to follow pregnancy.

Vascular factors.—A vascular factor in pancreatitis has been indicated both by such vascular and hemorrhagic phenomena as phlebitis, venous thrombosis, hemorrhage, purpura and blood coagulation aberrations which are associated with pancreatitis and by the experimental demonstration that interference with pancreatic blood flow not only may initiate pancreatitis but also may increase the extent of pathology induced by other etiologic agents. Thus, Popper *et al.* were able to convert pancreatic edema into pancreatic necrosis when, in addition to stimulating an obstructed gland, ischemia was induced by arterial ligation.

The mechanisms whereby interference with pancreatic blood flow has been assumed to occur in clinical pancreatitis include:

1. Venous stasis due to mechanical compression from edematous interstitial tissues. This mechanism must be rare since in mumps, where etiology is infectious in type, the pancreatitis is edematous in form, fat necrosis and hemorrhagic pancreatitis almost never supervening.

2. Venous thrombosis secondary to enzymatic or bile-induced venous inflammatory reaction.

3. Vascular spasm due to neurovascular reflex (viscerovisceral), to localized arteriolar inflammation as in periarteritis nodosa and lupus erythematosus, and to an antigen-antibody reaction.

4. Arteriolar obstruction due to sclerosis.

5. Arteriolar rupture due to arteriolosclerosis (pancreatic apoplexy) or to erosion by activated ferments.

6. Peripheral vascular shock.

The vascular factor is thought to be the operative agent in "minimal focal pancreatitis," in the pancreatitis associated with diabetic coma, in the "terminal acute pancreatitis" found incidentally at postmortem in elderly patients dying of other causes, notably coronary occlusion, and in the acute pancreatitis reported following aortography.

While it is obvious that the vascular factor as the sole initiating etiology of pancreatitis must be rare indeed, its role as a contributing agent and the one which may critically determine the extent of pathology is significant.

Toxic, allergic and unclassified factors.—Pancreatic toxins include such substances as methyl alcohol, alloxan, zinc oxide, cobaltous chloride and bacterial toxins. Although it is true that these substances can be used in the production of experimental pancreatitis, there is little evidence of their significance in the pathogenesis of human pancreatitis.

With the exception of a report by Shaffer, there has been no study implicating or evaluating allergy as an etiology in clinical human pancreatitis. Shaffer described three interesting cases in which the diagnosis of acute pancreatitis was made surgically, in which the attacks of abdominal pain were associated with elevations of the blood amylase, eosinophilia and generalized urticaria, and in which relief of pain and other symptoms was obtained with ephedrine and pyribenzamine. In the experimental field, Thal has produced pancreatitis by the Shwartzman and Arthus reaction. He is of the opinion that this mechanism, through its effect on pancreatic blood flow, may have some significance in clinical pancreatitis.

Among the miscellaneous clinical types of pancreatitis in which the mechanism is poorly understood are (1) the pancreatitis of pregnancy, (2) the pancreatic lesions in Hodgkin's disease and (3) the pancreatitis associated with electric shock therapy.

Traumatic pancreatitis.—Pancreatitis may follow external abdominal trauma and may manifest itself by the development of a palpable mass due to pseudocyst, by pleural effusion, by chylothorax and/or by elevation of the blood amylase. Pancreatitis has

also been observed to follow operative procedures such as splenectomy, sphincterotomy and subtotal gastrectomy in which pancreatic ferments are released locally into the tissues within and around the pancreas due to injury or obstruction in the pancreatic duct system or due to interference with its blood supply. On the other hand, pancreatitis has been observed following the surgery of organs at some distance from the pancreas. Such cases may have a vascular etiology.

Mechanism of Disease Manifestation

Pain and shock are the outstanding symptoms of acute pancreatitis; pain and metabolic disturbance dominate the clinical picture of chronic pancreatitis. Yet, all three—pain, shock and metabolic disturbance—may be absent as in "painless" pancreatitis also, the extent and degree of pathology cannot be correlated with the severity of symptoms. In fact, in some instances, the appearance of diffuse calcification is accompanied by moderate relief and appears to signify a subsidence of the inflammatory process.

The pain in acute pancreatitis results from distention of the pancreatic capsule, retroperitoneal extravasations, chemical peritonitis and obstruction or spasm in the pancreatic ducts, the extrahepatic biliary tract and the duodenum. The localization of pancreatic pain from different areas of the gland extends across the epigastrium from right to left in accordance with the position of pathology. Pain from any region of the pancreas may be transmitted to the midback. These pain patterns were derived from the experimental studies of Bliss *et al.*, who stimulated various portions of the gland with electrodes, and from the observations of Chapman *et al.*, who reproduced pancreatic pain by balloon distention of the biliary ducts, the duodenum and the upper small intestines.

The systemic effects in acute pancreatitis are presumed to result from the absorption of activated pancreatic ferments and the products of pancreatic digestion into the blood stream. Shock is the outstanding systemic phenomenon. It may be so profound that death supervenes within a few hours. The shock or "cardiovascular syndrome" in acute pancreatitis results from the combined effects of the following physiologic alterations:

1. Hypertrypsinemia, the presence of which is indicated by increases in the serum proteolytic activity and decreases in fibrinogen.

2. Hyperlipasemia, the presence of which is reflected by hyperlipemia and by fat necrosis in the subcutaneous tissue or in the bone marrow.

3. Alterations in blood coagulability with hemorrhagic and thromboembolic phenomena.

4. Marked contraction of the blood volume with deficits approaching 30% presumed to be the result of fluid exudation and hemorrhage.

5. Marked disturbances in the electrolyte balance, including lowering of the blood calcium, potassium and sodium levels. The depression of calcium is due to its fixation by fatty acids in areas of fat necrosis. When the blood calcium falls below 7 mg. %, tetany may be manifested. Tetany has even been reported in a patient with normal serum calcium level, in which case it is due to the binding of ionic calcium by the increased concentration of fatty acids in the blood. The hypocalcemic tetany of pancreatitis responds to the intravenous administration of calcium; the normocalcemic tetany does not, but is relieved by the administration of parathormone. The calcium levels in pancreatitis associated with hyperparathyroidism are unreliable indices. The changes in blood potassium and sodium are not well understood. They appear to be responsible, in part, for the abnormal electrocardiographic changes seen in acute pancreatitis.

6. Acute coronary insufficiency due to thrombosis and electrolyte disturbances.

7. Acute adrenal insufficiency due to stress or to actual bilateral adrenal hemorrhage. The steroid deficit may play a role in the development of electrolyte imbalance.

In the nonfatal cases, evidences of other metabolic derangements can be uncovered. Disturbances of insular function cause hyperglycemia, glycosuria and impaired glucose tolerance in about 50% of the cases when these parameters of carbohydrate metabolism are studied. These changes, though transient in the acute case, with repeated attacks, may progress to a true "pancreatic" diabetes.

Inflammatory and degenerative changes can be demonstrated pathologically in the liver; abnormal cephalin flocculation, hypo-

prothrombinemia and depression of the blood fibrinogen are other evidences of liver damage. Jaundice is seen in about 25% of patients with acute pancreatitis. In addition to hepatic inflammation, jaundice may result from sphincter stenosis, from obstruction of the terminal common duct as it traverses an edematous pancreas and also from concomitant exacerbation of pre-existing biliary tract pathology. Reversible impairment of gallbladder function during acute pancreatitis has been suggested.

Alterations in lipid metabolism during acute pancreatitis are poorly understood. Hyperlipemia and grossly fatty serum have been regularly observed. Lynch has cited patients in whom there was evidence of widespread embolization and lipoid nephrosis; others have reported panniculitis and disseminated fat necrosis in the marrow.

Focal necrosis in the skeletal muscle, the heart and within the cerebrospinal system are manifestations of toxic reactions to the pancreatic ferments and of acute vitamin deficiencies. Avitaminosis D has been implicated in the osteomalacia of pancreatic disease.

Pulmonary atelectasis and pneumonia due to abdominal distention and pleural effusion occur frequently. Severe pleurisy has been seen in those patients in whom the pleural exudate contains high concentrations of pancreatic enzymes. These ferments are thought to reach the pleural fluid from the ascitic exudate by passage through transdiaphragmatic lymphatic channels.

The vascular phenomena in acute pancreatitis include peripheral hemorrhage, thrombosis, thrombophlebitis and altered blood coagulation. Although hypertrypsinemia and alteration of liver function have been credited with the induction of these phenomena, many physiologic facets of the hematologic and vascular effects remain to be explained.

Laboratory Aids in Diagnosis

No laboratory study can replace the clinical suspicion of acute pancreatitis, but, once suspected, several laboratory methods may be helpful.

Blood enzyme levels.—Determination of pancreatic ferment concentrations in the blood is the most common and useful

laboratory diagnostic procedure in general use. *Serum amylase* is the most conveniently measured enzyme. The amylase normally present in the blood is derived from the pancreas, the salivary glands, the liver and other tissues. There is some evidence that the normal blood amylase is under endocrine control, is sensitive to alterations in the rate of carbohydrate metabolism and that the site of one mechanism regulating its level in the blood appears to be the liver. Decreases in blood amylase have been observed under conditions of adrenocortical stress, in hepatocellular disease, in advanced pancreatic parenchymal destruction and following the administration of propylthiouracil. The increases in serum amylase content seen during the course of acute pancreatic inflammations and/or ductal obstructions derive wholly from the pancreas, either by retrograde passage due to back pressure or by some alteration in cellular orientation of enzyme secretion.

Elevations of serum amylase above the statistically derived normal range occur in acute pancreatitis during the first 72 hours of illness. In the milder inflammations, small rises may be present for only a few hours, making it imperative for early and frequent amylase determinations during the initial period of illness. Not infrequently, a drop to normal ranges may take place rapidly, indicating early resolution. On the other hand, sudden decreases in serum amylase may reflect extensive destruction of the pancreas with subsequent cessation of amylase production. For these reasons, it is not possible to correlate the severity of pathology with the degree of elevation of the blood amylase, nor need a normal amylase exclude the diagnosis of pancreatic disease. A similar statement would be justified for all other pancreatic enzyme determinations with the exception of the as-yet-unsubstantiated claim for serum desoxyribonuclease I activity. Marked and protracted serum elevations of the latter enzymes have been noted only with pancreatic necrosis; in pancreatic edema, the rise was temporary and minimal.

Blood amylase elevations have been reported in a number of situations in which there is no pancreatic affection. These include gallbladder disease, choledocholithiasis, biliary dyskinesia, perforated peptic ulcer, intestinal obstruction, bowel transection, ruptured ectopic pregnancy, uremia, after cholangiography, after

morphine-like narcotics and after parasympathomimetic drugs. In uremia, the blood amylase rise is due to diminished excretion into the urine. Concomitant renal insufficiency, in fact, may be responsible for persistent elevation of amylase in patients with acute pancreatitis, but, in general, it is possible to distinguish the hyperamylasemia of uremia from that due to pancreatitis by determining the rate of amylase excretion in the urine. In uremia, this is low; in pancreatitis, the urinary amylase is high. The elevations of blood amylase in extrapancreatic diseases and following medication, though disquieting, are minimal, rare and hardly detract from the general usefulness of amylase determinations.

Serum lipase elevations tend to parallel blood amylase rises, but lipase increases occur later in the course of acute pancreatitis and tend to persist longer than amylase elevations. High lipase has been reported in a number of patients with pancreatic cancer in whom the blood amylase was normal.

The lipase determination is of considerable significance in *mumps*. Strictly speaking, blood amylase rises, even in the presence of abdominal pain, cannot confirm the presence of pancreatitis in mumps since this enzyme is contributed to the blood stream by the inflamed salivary gland; only lipase rises are diagnostic. There is considerable confusion concerning the real incidence of pancreatitis in mumps. Obvious clinical pancreatitis occurs in 2.4% of the patients. Elevations of the blood amylase have been reported in 80–90%, but this, as stated, does not necessarily indicate pancreatitis. Poppel and Bercow observed roentgen evidence of pancreatitis in 50% of the patients examined by barium meal. Lipase elevations have ranged from 12%, which would suggest that pancreatitis has a relatively low incidence in mumps, to 73%, which leads to the conclusion that pancreatitis might be considered an integral manifestation of a virus infection of the serozymogenous glands throughout the body.

The serum lipase determination, although it appears to complement and extend the usefulness of the serum amylase test, has not gained widespread use. One reason for this is the complexity of chemical estimation and the excessive length of analysis time, which varies from 6 to 12 hours, depending on the substrate used. Another factor is the lack of standardization for this procedure

which often fails to distinguish between the lipolytic activity of the serum due to esterase and that due to specific pancreatic lipase. Finally, there have been a number of false positive serum lipase elevations in patients with hepatic and biliary tract disease, intestinal obstruction and following the administration of opiates.

Urinary enzyme levels.—Elevation of the *urinary amylase* concentration has been used to diagnose acute pancreatitis. Amylase is excreted by the kidney as a threshold substance. Thus, elevations in blood amylase are reflected in the urine, although the appearance of rises in the latter may be delayed by the presence of renal insufficiency. Although it has been claimed that elevation of urinary amylase levels may persist long after the disappearance of high concentrations of amylase in the blood, many have found such wide variation of urinary amylase concentration, even in the normal subject, that the value and reliability of this determination have been seriously questioned. It has been suggested that more significant data might be obtained if urinary amylase data were determined quantitatively as a rate of secretion rather than qualitatively. This suggestion is supported by the studies of Saxon *et al.*, who have concluded that urinary amylase secretion rates are more significant than urinary amylase concentration, that elevations in urinary amylase secretion rate is superior to blood amylase elevation in the diagnosis of acute pancreatitis, and that urinary amylase secretion rates are more closely correlated with the clinical course than blood amylase levels.

Although lipase levels in the urine have been studied in the past, little was done to utilize these determinations as a diagnostic test until recently, when Nothman reopened the subject and indicated such a possibility. It was shown experimentally that lipase in the urine was of pancreatic origin, that it increases following mecholyl or secretin, and that it disappears following pancreatic resection. In a clinical study of normal subjects, the lipase concentration and 24-hour content was found to change only slightly under varying conditions. In subjects with pancreatic cancer or fibrotic pancreatitis, the quantitative increase in urinary lipase excretion following intravenous secretin was significantly less than that observed in normal subjects.

Blood chemical determinations.—Transitory *glycosuria* and

hyperglycemia have been observed in about 10% of cases of acute pancreatitis and in acute exacerbations of chronic pancreatitis. The true incidence is higher; we have found glycosuria, hyperglycemia and/or abnormal glucose tolerance in 25% of an unreported series of more than 100 patients with acute pancreatitis. Hyperglycemia without glycosuria is particularly suggestive of pancreatic inflammation. *Latent diabetes,* as evidenced by abnormal glucose tolerance, and overt pancreatic diabetes have a frequency approaching 50% in patients with cancer in the tail or body of the pancreas and in advanced cases of chronic pancreatitis. Doubilet believes that the brittleness of "pancreatic diabetes" is due to an insulin sensitivity resulting from simultaneous loss of alpha and beta cell functions. Unfortunately, disturbances in carbohydrate metabolism are so prevalent in patients without pancreatic inflammatory or neoplastic disease that these findings are only suggestive—never diagnostic.

Blood calcium depressions to values below 7.0 mg. % have been associated with *tetany* and fatal outcome. Lowered values of serum calcium have been reported to persist for a fortnight or longer and, thus, are thought to have diagnostic significance in patients with acute pancreatitis who are seen after the blood amylase has returned to normal. This suggestion must be judged in light of the low serum calcium values which have been reported in perforated peptic ulcer and also in light of the possible masking potentialities which may exist in those cases associated with hyperparathyroidism. Lowered *potassium concentrations* to levels below 4.0 mEq./L. have been observed and attributed to lowered intake, excessive urinary loss, loss by nasogastric suction and to alteration in adrenocortical function.

Roentgenographic methods.—The pancreas, being a soft-tissue structure and its duct system undelineable in the intact patient, does not lend itself easily to direct roentgen study except by special technics such as transverse axial stratigraphy, which uses oblique projections, and the combined method of gaseous distention of the stomach and retroperitoneal space, which uses oxygen as a contrast medium. To be sure, some pancreatic lesions can be recognized readily by virtue of calcification within the gland, as in chronic calcareous pancreatitis, or within pancreatic cysts or pseudocysts, in which calcium is deposited in the cyst walls.

The roentgen manifestations of acute pancreatic inflammation include: (1) haziness in the flat film of the abdomen, (2) obliteration of the psoas outline, (3) elevation of the left diaphragmatic leaf, (4) paralytic ileus with its manifestation of the sentinel jejunal loop in the left upper quadrant and/or the colon-cutoff sign and (5) basal pneumonitis, pleurisy or pleural effusion in the left chest. If oral barium is given in the milder cases, elevation of the stomach and widening of the retrogastric space due to generalized enlargement of the pancreas may be detected.

Cholecystography (oral), except for the demonstration of calculi, usually offers little assistance in acute pancreatic inflammation because of concomitant impairment of gallbladder function.

Peritoneal aspiration.—Howard, Keith and others, and recently Pfeffer and others, have stressed peritoneal tap as an important aid in diagnosis. When hemorrhagic or beef broth fluid is obtained from the left lower quadrant, there is a strong indication of pancreatitis. The demonstration of high amylase levels within this fluid fortifies this conviction, but cannot be accepted as absolute proof of pancreatitis, since equally high levels have been observed by Berk and others in the ascites of patients with bile peritonitis and perforated peptic ulcer. Pancreatic ferments have also been reported from the pleural fluid and have been found in cysts of organs other than the pancreas, viz., ovarian cysts.

Therapy

The immediate problem of management of acute pancreatitis is the choice between medical and surgical treatment. When the diagnosis has been established, the overwhelming evidence based on comparison between the mortality of patients treated surgically, which ranges from 35 to 78%, and the mortality of patients treated medically, which appears to vary between 10 and 20%, favors medical management.

In those patients in whom laparotomy has been done because of inability to make a positive diagnosis, surgical manipulation should be reduced to a minimum: drainage of the lesser sac or a diversionary operation on the biliary tract, cholecystostomy or choledochostomy in patients with obvious biliary tract disease.

Medical treatment should be energetic whether the clinical picture is mild or severe, for it is not possible to predict which cases will regress rapidly and which will progress to critical complication. Therapy in the acute stage is directed toward: (1) treatment of pain, (2) treatment of shock and electrolyte imbalance, (3) management of carbohydrate metabolism disturbances, (4) treatment of ileus and control of distention, (5) prevention of suppuration, (6) suppression of pancreatic secretion and neutralization of ferment activity, (7) management of surgical complications and (8) prevention of recurrence.

Treatment of pain.—Morphine and other opiates may effectively relieve pancreatic pain, but their stimulation of sphincter tone may intensify the anatomic basis for pancreatitis at the very moment of temporary symptomatic relief. Demerol® and papaverine, having less effect on smooth muscle, are less dangerous in this regard.

Spasmolytic drugs not only effectively relieve pain, but at the same time induce relaxation of the sphincter of Oddi. These agents, including nitrites, atropine, hexamethonium and Banthine®, must be used with due caution in patients suffering from severe shock or with evidence of myocardial insufficiency. Banthine® appears to be the drug of choice in relief of pain because of its additional pharmacologic effects, which include suppression of gastric acidity and thus, indirectly, diminution of endogenous secretin, relaxation of the sphincter and minimal inhibition of pancreatic enzyme secretion.

Intravenous procaine hydrochloride has been used to relieve pain in pancreatitis through its local anesthetic, central analgesic, antihistaminic and antispasmodic actions, but dangerous circulatory and respiratory side-reactions limit its use. Nerve block and epidural block, either fractional or continuous, have been tried with some success. Gage and others have used paravertebral sympathetic block and splanchnic block for analgesia. Relief of pain is due to interference with afferent fibers from the pancreas, to some lessening of pancreatic secretion and possibly to an increase in blood supply to the pancreas which prevents the conversion of edema to necrosis. The use of such measures has been advocated only in conjunction with other therapies and not as a substitute.

Treatment of shock and electrolyte imbalance.—Every effort should be made to overcome the shock of acute pancreatitis, which is always an outstanding complaint and often disproportionately severe in comparison with other signs and symptoms. The extent to which the blood volume is decreased and the beneficial effects which its restoration by whole blood, serum albumin and other substitute expanders have on the course of clinical and experimental pancreatitis have been appreciated only during the past few years. The marked fall in initial mortality in medical cases during the past decade is probably due to strict attention to the correction of shock.

Deficits in the serum sodium, potassium and calcium derive not only from the inherent physiologic disturbances in acute pancreatitis, but also from diminished intake, removal by nasogastric suction and physiologic loss in exudation and intestinal secretion. These deficits must be corrected in order to maintain normal blood volume, normal blood pressure and adequate glomerular filtration by infusion of electrolytic solutions, but always with due regard to renal function. Occasionally, parathyroid hormone is necessary to elevate blood calcium when intravenous calcium is unable to do so. The administration of potassium should always be carefully controlled, lest hyperkalemic toxicity occur.

Management of carbohydrate metabolism disturbances.—Glucose must be administered cautiously, for it may aggravate a diabetic state precipitated by acute pancreatitis. When hyperglycemia and glycosuria are marked and diabetic acidosis imminent, small doses of insulin must be given. Large amounts of insulin are rarely required and are quite dangerous, since the diabetic state in acute pancreatitis is labile; a reactive hypoglycemia is undesirable, for it acts as a potent stimulus to pancreatic enzyme secretion.

Treatment of ileus and control of distention.—The treatment of ileus and control of abdominal distention are accomplished by stopping oral intake and by the use of nasogastric suction. These measures contribute to the suppression of pancreatic secretion by removing hydrochloric acid from the stomach and so diminishing the acid-secretin mechanism and also by preventing the flow of pancreatic juice, which might be stimulated by the presence of foodstuffs in the duodenum. The net result is a "splinting of the

pancreas" and an interference with the pathogenetic cycle which produces additional pathology.

Prevention of suppuration.—The prevention of suppuration and the late infectious complications of pancreatitis can be accomplished by the use of the broad-spectrum antibiotics, penicillin and tetracycline. The liberal use of chemotherapy has all but eliminated the late deaths in acute pancreatitis by preventing abscess formation in the lesser sac, in the subphrenic spaces and in the pancreas. If a patient survives the initial phase of illness, mortality is unlikely, morbidity minimal and rapid recovery the rule.

Suppression of pancreatic secretion.—Measures to suppress the pancreatic secretion include the withholding of food, nasogastric suction, sympathicolytic procedures and drugs, and irradiation of the pancreas. Recently, inhibition of pancreatic secretion at the cellular level by Diamox® has been proposed as a therapeutic measure in acute pancreatitis. Popper *et al.* did not find this drug effective in experimental pancreatitis, but there have been reports of its value in inhibiting pancreatic secretion in pancreatic fistulas. Diamox® awaits a critical trial in human pancreatitis.

Control of the toxicity and the local pathology of pancreatitis has been attempted with the use of substances which specifically inhibit the activated pancreatic enzymes. Soybean trypsin inhibitor has been used with success by Coffey and others to lessen shock, but its administration is not without danger. Popper, Hoffman, and others, however, noted no effect of this trypsin inhibitor on the morbidity and mortality of experimental pancreatitis. The antitryptic action of serum albumin has also been discounted. Popper believes that the importance of activated lipase in systemic toxicity and local pathology has not been fully appreciated, and he has observed some benefit in experimental pancreatitis from the use of a lipase inhibitor.

Management of surgical complications.—The surgical complications which arise in acute pancreatitis include abscess, which necessitates drainage, pseudocyst, which requires diversion into the gastrointestinal tract, pancreatic fistula and the complications inherent in coexisting biliary tract disease.

Pancreatic abscess is a rare complication since the advent of chemotherapy. This may occur, as previously stated, in the

parenchyma, lesser sac and in the left subphrenic space. The surgical problem is not drainage, per se, because this ordinarily can be done without technical difficulty, but rather it is the possibility of subsequent formation of a pancreatic fistula with the attendant deleterious effects of electrolyte loss, disturbance in metabolism and maceration of the skin.

Pancreatic fistulas have been treated by sclerosing agents, total excision whenever possible, implantation into the stomach or jejunum and by fistulojejunostomy in Roux-Y fashion.

Pancreatic cysts or pseudocysts are treated when, by virtue of size and situation, symptoms are produced by encroachment on other organs. It is remarkable how often large pseudocysts will suddenly disappear without operation. The ideal procedure would be extirpation by excision, but this is not always feasible, especially in head lesions, and is not always desirable because of the extent of surgery involved. Simple evacuation and external marsupialization have been discarded because of the high incidence of recurrence and because of the frequent development of external pancreatic fistulas. Internal drainage may be accomplished by anastomosis of the cyst to the stomach, the duodenum or jejunum, or by what is accepted by most to be the procedure of choice, a cystojejunostomy using a Roux-Y anastomosis to eliminate the hazard of intestinal regurgitation into the cyst cavity.

Prevention of recurrence.—There are three measures which may be of value in prevention of recurrent attacks of acute pancreatitis following an initial single episode: (1) the avoidance of gluttony, (2) the interdiction of alcoholic intake and (3) the eradication of biliary tract disease if it is found to be present. Fortunately, when these measures are observed, most patients with acute pancreatitis recover without clinical or functional residua and have no further pancreatic inflammations. There is no evidence at present which would completely justify any surgical procedure on the patient without biliary tract disease whose symptoms completely subside with the expectation that such a surgical measure would prevent subsequent attacks.

When pancreatitis is associated with other metabolic disorders, efforts of course should be made to control these: essential hyperlipemia by dietary control of fat intake, diabetic coma, hyperparathyroidism.

CHRONIC PANCREATITIS

Under this term are included all the varieties of recurrent chronic inflammatory diseases of the pancreas. Although conventionally assumed to be variants of one entity, and to result from repeated episodes of the acute variety of the disorder, there is some evidence that this is a gross oversimplification of the problem.

In our experience, it is extremely rare for the person who presents with the first episode of acute pancreatitis to go on to the chronic relapsing form. This, of course, may simply mean that acute pancreatitis is common and the recurrent forms extremely uncommon. On the other hand, there are people who may present with far-advanced symptoms of chronic inflammatory disease (calcification, diabetes mellitus and malnutrition) who may never have had a clinically recognizable acute episode. Interestingly enough, these seem to be increasing recently.

Varieties of Chronic Pancreatitis

The clinical features of the classic form of *chronic relapsing pancreatitis* are well known, especially since their description in America by Comfort and his associates. Predominantly a male disorder (ratio of 2.5:1), occurring in the 4th decade and after, it usually manifests itself with recurrent attacks of upper abdominal pain in the area of distribution of pancreatic pain. For many, this pain is its only manifestation, but the chronicity, recurrences and failure to respond to simple analgesics often result in the complete incapacity of these unfortunate people and all too frequently leads to their addiction to morphine or Demerol®. When the destructive inflammatory changes within the gland are extensive enough, there result the classic metabolic defects of this disease: calcification, impaired carbohydrate metabolism (a true pancreatic diabetes) and external pancreatic insufficiency leading to malabsorption and malnutrition.

In this setting, it is conventional to emphasize two associated disorders: chronic gallbladder disease with stones and chronic alcoholism.

Of the first of these, cholecystic disease, clinical or radiographic

evidence may be present in perhaps 25% or less of the patients, depending on where the series is collected. A considerable number of patients with chronic pancreatitis (especially in large city hospital populations, up to 40%) may also be chronic alcoholics. The possible metabolic and mechanical roles of alcohol in this disorder have been discussed previously in this article, but there are many interesting and puzzling aspects of this association. Fibrosis of the pancreas may frequently accompany alcoholic Laennec's cirrhosis, yet outspoken chronic relapsing pancreatitis in our experience rarely accompanies outspoken portal cirrhosis with portal hypertension.

"Silent" pancreatitis.—A variant of this disease or diseases is the patient who is accidentally discovered to have extensive calcification of the pancreas during life when a flat plate of the abdomen is taken for any reason at all. We have seen this in persons without antecedent history of biliary disease or alcoholism, who have had no episode at all remotely resembling acute pancreatitis in the past. Not only may they be clinically quite well, but study of their external pancreatic function, balance studies and glucose tolerance reveal no significant impairment of either the exocrine or endocrine pancreas by usual criteria. It may be questioned whether this may properly be considered "pancreatitis" at all. Yet profound pathologic changes may be presumed to have taken place in the gland. The calcification is not simply precipitation of stores within ducts or duct-like structures, but would appear to be a diffuse calcinosis of the gland itself.

Such a conclusion seems justified from the discovery at postmortem of interstitial inflammatory or focal pancreatitis in a wide variety of clinical conditions, without antecedent symptomatology to suggest acute pancreatitis during life. This finding, however, does not justify the indiscriminate diagnosis of pancreatitis in all people with ill-defined upper abdominal pain or digestive disturbances.

Hereditary pancreatitis.—Our ideas of the nature of pancreatitis have been further enlarged by the studies of Gross and Comfort of a hereditary variety, occurring in several kinships, usually starting in childhood or early adult life which behaves as a non-sex-linked mendelian characteristic. Their contribution to the genetic aspects of the disease has disclosed also a heritable

defect in the pattern of urinary amino acid excretion in these patients and their relatives: an increased excretion of the amino acid lysine. At present, the relationship between the pancreatic disorder and the increased amino aciduria is unknown, but it does stress the genetic and metabolic aspects of the disease.

Hyperparathyroidism, hyperlipemia and pancreatitis.—The possible metabolic nature of this group of disorders has been further enlarged by the association of pancreatitis with two other metabolic disorders: hyperparathyroidism and essential hyperlipemia.

Diagnosis

So far, we have discussed the historical concepts and varieties of etiologic forms of chronic pancreatitis. If we are to make the diagnosis clinically, we must bear this entity in mind in all situations of obscure upper abdominal discomforts; on the other hand, we cannot use chronic pancreatitis as a catch-all for every upper abdominal undiagnosed pain. In the truly "silent" pancreatitis, we will get no assistance from the history, of course, whereas in the other clinically significant varieties the history is a starting point. The classic features are recurrent upper abdominal pain, distributed over the area of radiation of the pancreas, often to the back. The picture of severe prostrating pain of acute pancreatitis rarely occurs in chronic pancreatitis, although the patients are frequently disabled. The history of chronic biliary disease or of chronic excessive consumption of alcohol may be helpful. In view of the other varieties of chronic pancreatitis, history-taking must now be directed toward evidence of a familial nature. A history suggestive of hyperlipemia in the family or in the patient, or features suggestive of hyperparathyroidism, should be looked for specifically. When the inflammation of the pancreas is so severe as to lead to disturbances in the external secretion of the pancreas, one then may begin to elicit features suggestive of malnutrition and diabetes mellitus. This aspect is a late feature of the disease. Malnutrition is manifested first by calorie loss with consequent weight loss and secondly the passage of large, bulky, foul-smelling stools, containing large amounts of neutral fats. This is also accompanied by evidences of malabsorption of

fat-soluble vitamins; however, osteomalacia and evidences of hypoprothrombinemia are exceedingly rare.

Physical findings.—Physical examination may disclose nothing. In other instances, there may be evidence of marked weight loss. If the patient has hyperlipemia, there may be evidence of xanthomata. Abdominal examination may disclose nothing, there may be tenderness over the area of the pancreas; in rare instances, a mass such as a pseudocyst may be found in the pancreas. In general, it is the history and the laboratory findings which establish the diagnosis, rather than the physical findings.

Laboratory studies.—A plain film of the abdomen may be helpful when disclosing the presence of calcification within the pancreas. Despite the considerable argument that exists at present, it may be said that these calculi are either in the ducts or in the acinar tissue itself. The bulk appear to be within acinar tissue. A small-bowel x-ray is also useful in patients who have evidence of malabsorption, in that patients with a chronic pancreatitis have a normal small bowel pattern, in contrast to disordered motor pattern seen in patients with idiopathic sprue. Chemical studies play a significant role in the diagnosis of chronic pancreatitis. If the disease is far advanced there is evidence of disturbance of carbohydrate metabolism: elevated fasting blood sugar, an abnormal glucose tolerance test and glycosuria. This feature, however, may be missing in some instances. The study of blood enzymes of pancreatic origin is not particularly helpful in the diagnosis. During acute exacerbations of chronic pancreatitis, there may be a rise in serum amylase, but usually the serum amylase level is either normal or low; the same is true of lipase. A wide variety of newer enzyme determinations has been proposed, but none of these have yet met satisfactory clinical judgment. If there is marked impairment of external pancreatic secretion, evidence for this may be sought in the examination of the stools, both grossly and by chemical tests when there is steatorrhea composed essentially of neutral fat. In our experience, about 30% of patients with chronic pancreatitis have this far-advanced evidence of external pancreatic secretion. Therefore, when the patient does not have calcification or diabetes or steatorrhea, one is hard put to make the diagnosis of chronic pancreatitis, at least to substantiate it when it is suspected clinically,

unless there is direct study of the external secretion of the pancreas. There is a place for the use of fat and oleic acid labeled with I^{131}, when the differential diagnosis lies between pancreatic and idiopathic steatorrhea. Here, the published evidence indicates that the absorption of oleic acid may proceed normally, while triolein absorption is impaired in the presence of external pancreatic insufficiency. But this test can logically be applied only to those patients presenting advanced evidence of external pancreatic insufficiency. In our experience, a large number of patients with chronic pancreatitis would be missed if this were relied on. For this reason, we place much emphasis on the study of the external secretion of the pancreas by direct duodenal intubation. The secretin test as performed by our group consists of intubating the duodenum by a double-lumen tube, which effectively separates pancreatic secretion stimulated by secretin from contamination by hydrochloric acid. A standard dose of secretin is used (1 unit per kilogram of body weight), and the secretions are collected for a period of 80 minutes, at the end of which time response to secretin has been dissipated. On the basis of extensive study of normal persons, statistical levels have been established for a normal response. At present, there is no evidence of a syndrome of hypersecretion of the pancreas. Therefore, the statistical norms have been devoted to establishment of the lower limits of the normal. When the values have been adjusted to the body weight, there is considerable reduction in scatter. These values include volume flow, which is essentially greater than 2.0 cc. per kg. of body weight in normals, bicarbonate concentrate of above 90 mEq./L., with a wider variation in amylase which may be anywhere from 6 to 9 units of amylase per kg. of body weight. We have observed that reduction in flow may occur in some patients with chronic pancreatitis, but that their striking defect is a marked inability to elaborate a fluid of high bicarbonate content as well as depression of enzyme output. From these criteria, we feel that we are able to assess the external secretion of the pancreas for volume flow, bicarbonate and enzyme (amylase) with a high degree of reproducibility and reliability.

Summary: Chronic pancreatitis can be suspected clinically only on the basis of recurrent upper abdominal pain associated with malnutrition, diabetes and steatorrhea. The physical findings are

not particularly helpful. The laboratory findings of pancreatic calcification, impaired carbohydrate tolerance and increased excretion of fat in the stool are all supportive. A final diagnostic statement as to external pancreatic function, it appears to us, depends on the study of the external function directly by collection of pancreatic juice under standard conditions. It remains to be determined whether the addition of the hormone pancreozymin will improve the diagnostic value of the secretin test. An important part, however, in the current secretin test is the cytologic examination of the fluid, since the picture of chronic pancreatitis may often be mimicked by a carcinoma of the body of the pancreas. Since, indeed, carcinoma may exist in the presence of chronic pancreatitis, we have found the examination of the cells of this fluid extremely helpful. In our experience, duodenal cytology is much easier, much more feasible, and the cells are better preserved than in gastric cytologic studies.

Therapy

The treatment of chronic pancreatitis is difficult, far from standardized and often disappointing. Medical therapy, which leaves much to be desired, includes a high-calorie, high-protein, low-fat diet supplemented by vitamins. Small frequent feedings are advocated to minimize pancreatic secretion. Alcohol is interdicted because of its known and unknown effect on pancreatic secretion, and its action on the duodenal mucosa and sphincter. Substitution therapy includes pancreatic extract in patients with steatorrhea. Pancreatin sometimes strikingly reverses the symptoms of external pancreatic enzyme deficiency, but extremely high doses must be used (3–5 Gm. with each meal). In patients with gastric hypersecretion, an antacid serves to minimize acid inactivation of the replacement therapy.

Despite all forms of medical treatment, some patients continue to have excruciating pain, progressive weight loss and progressive mental and physical deterioration. Surgery is a final, often desperate, therapeutic attempt, and the many procedures that have been advocated are an index of the diversity of opinion about the pathogenesis of symptoms and of the indifferent success of such treatment.

The first point of attack is the underlying biliary tract disease which may be present. Removal of a diseased gallbladder produced a remission in about a third of one series of cases. The initial operation is the logical time to explore the common duct and to determine whether stone or inflammation is causing obstruction at the papilla.

Procedures for obstruction of the distal common duct are dictated by the site and type of obstruction. Stones are removed and prolonged drainage of the common duct is instituted. For ductal stenosis, choledochoduodenostomy or a Roux-Y choledochojejunostomy is thought to be superior to T-tube drainage, since the former completely divert the biliary flow from the pancreatic tract and by-pass lesions at the papilla. Roux-Y anastomosis minimizes retrograde regurgitation of intestinal contents into the biliary tree and therefore may be accompanied by a lower incidence of cholangitis and cholangiolitis and resultant biliary cirrhosis, than does direct ductal-enteric union.

Functional and organic obstruction of the periampullar region may be relieved by operations on the sphincter of Oddi. The original endocholedochal procedure, though feasible, has been discarded because occasionally the sphincter fibers are not interrupted and because fatal hemorrhage may occur. Transduodenal sphincterotomy has proved safer and more effective.

Neurosurgeons have devised procedures designed to relieve the debilitating pain of chronic pancreatitis and to diminish pancreatic secretion. Among advocated measures are stripping of the choledochal nerves from the common duct, splanchnicectomy and sympathectomy with and without splanchnic section. Section of the vagus nerve has been combined with some of the procedures mentioned because of its spasmolytic action on the sphincter muscle and its inhibitory effect on gastric, and possibly on pancreatic, secretion. Although interference with the autonomic nerves may afford palliation of symptoms, the experimental and clinical evidence suggests that it does not affect the progress of the disease.

Gastrointestinal diversion may be necessary because of mechanical obstruction of the duodenum, resulting from extensive fibrosis or from actual encroachment by a large cyst in the head of the pancreas. Cattell and Warren advocate gastroenterostomy for the

relief of such obstruction and combine it with vagus nerve section. Richman and Colp advised bilateral vagisection to supplement the effect of the gastrectomy and base their treatment on the theory that it provides a "splinting" of the pancreas by suppressing gastric acid secretion and diminishing endogenous secretion formation.

The direct surgical attack on the diseased pancreas includes operations designed to treat the complications of the inflammatory process, procedures attempting to eradicate etiologic factors which initiate the recrudescences of inflammation, and measures aimed at removing the diseased tissue itself.

Purulent collections within the pancreas, the lesser sac and the left subphrenic space are treated by incision and drainage. The threat of spreading peritonitis and pancreatic fistulization is minimized by the use of chemotherapy and drugs, such as Banthine®, which depress pancreatic secretion. Pancreatic cysts or pseudocysts require surgery only when, because of size or location, symptoms result from encroachment on adjacent viscera. Extirpation, the definitive treatment, is not always possible, especially in lesions of the pancreatic head; and, if feasible, is not always desirable because of the extensive surgery required for excision. Evacuation and marsupialization on the skin have been discarded, both because of recurrences and because of subsequent development of an external pancreatic fistula. Internal drainage by simple anastomosis of the cyst to the stomach, to the duodenum or to the jejunum by a Roux-Y cystojejunostomy obviates the nuisance of external drainage and the loss of pancreatic juice and electrolytes. These procedures return the pancreatic enzymes to the intestine. The hazard of regurgitation of chyme into the cyst cavity is lessened by the Roux-Y anastomosis.

A number of procedures designed to overcome pancreatic duct obstruction have been suggested, but have not had sufficient clinical trial to warrant conclusions on their value. Among these are pancreaticolithotomy, ligation of the main pancreatic duct so as to destroy completely the acinar tissue, and transection of the main pancreatic duct followed by immediate reanastomosis to the duodenum. Relief of pancreatic duct obstruction in a retrograde fashion has been attempted by implanting the tail of the pancreas or the distal end of the pancreatic duct into a loop of

upper jejunum. DuVal's caudal decompression of the pancreas seems a sensible solution of the problem of obstruction in the duct system distal to the sphincter, when this can be demonstrated convincingly.

Pancreatectomy is the final, desperate step reserved for those incapacitated persons in whom all other measures have failed. Resections of the left half of the pancreas in those rare cases in which the disease is limited and more severe in the tail presents no technical difficulty, and the results are gratifying. In most patients, however, the disease process is more diffuse and most severe in the region of the head. Distal pancreatectomy is of doubtful benefit in such cases, and total pancreatectomy is required. Total pancreatectomy, implying as it does resection of the duodenum and a choledochal anastomosis, is an operation of such magnitude and high mortality that many hesitate to advocate this procedure for a nonmalignant lesion. The diabetes and metabolic disturbances which follow pancreatectomy pose problems which may be no more easily managed than the pancreatitis itself.

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